CLINICAL PHARMACOLOGICAL EVALUATION IN DRUG CONTROL

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QUALITY OF CARE AND APPROPRIATE TECHNOLOGY

By the year 2000, there should be structures and processes in all Member States to ensure continuous improvement in the quality of health care and appropriate development and use of health technologies.

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CLINICAL PHARMACOLOGICAL EVALUATION IN DRUG CONTROL

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ABSTRACT

Some countries in the WHO European Region lack both the hard currency to import drugs and the raw materials for domestic production, while others wish to rationalize drug use for economic and other reasons. This makes the selection of drugs for appropriate therapy an important issue; it formed the central topic of the Eighteenth European Symposium on Pharmaceutical Evaluation in Drug Control. The participants discussed ways to select drugs, the promotion of more rational prescribing patterns by providing better information to prescribers, ways to ensure the quality of clinical trials of drugs, and the harmonization of drug promotion with rational drug use. The Symposium participants made recommendations on the principles, content and implementation of the drug selection process and on the need for information and education for health professionals patients and people involved in drug policy and regulation. Other recommendations called for action from countries and WHO to improve both clinical trials and the information given in promotional material for both prescription and nonprescription medicines.

Keywords

DRUG EVALUATION
CLINICAL TRIALS
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CONTENTS

Introduction

Political changes in the countries in the central and eastern parts of the European Region have led to an acute shortage of imported drugs, owing to a lack of hard currency, and some of these countries also lack the raw materials required to produce drugs for themselves. The quality of prescribing is another issue of importance, and one that all European countries must address, regardless of the strength or weakness of their economies. Governments are no longer prepared to pay for unnecessary or inappropriate drug treatments. Wise drug selection is therefore vital in all the countries of the European Region.

The Eighteenth European Symposium on Pharmacological Evaluation in Drug Control was held in Bad Neuenahr, Germany, from 10 to 13 December 1991. The working papers and the participants are listed in Annexes 1 and 2, respectively. The aims of the Symposium were:

- to develop recommendations for countries to use in selecting drugs, promotiong the idea of selective prescribing to the health professions and the public, and ensuring the ethical and scientific quality of clinical trials; and
- to develop guidelines for bringing drug promotion into line with the idea of selective prescribing.

Discussion

Problems in central and eastern Europe

Drug production, control and research in the central and eastern parts of the Region have suffered from the rapid political and economic changes since 1989. Although the members of the Council for Mutual Economic Assistance (CMEA) had cooperated closely on pharmaceuticals production, this cooperation ended in January 1990. Apart from the general economic crisis, raw materials have been insufficient to satisfy national demands. In addition, there were no resources for structural or functional changes, the most important of

which was independence from central government control. Finally, most pharmaceuticals plants produced an inefficient range of products and could not meet the demands of good manufacturing practice. To a great extent, this situation persists.

While pharmaceuticals wholesalers and retail pharmacies are being privatized in some countries, they remain run by the state in several others.

All countries are developing new national policies and laws on drugs. The latter are particularly necessary, as these countries had lacked drug laws. Price control is another area that is being radically restructured. In the past, prices were set arbitrarily and bore no relation to production costs. Now, pricing policies are being established, favouring the development of local industry, facilitating drug imports and requiring co-payment by patients.

Further, drug control is being reorganized to implement a rational registration policy, ensure a supply of essential drugs and organize and supervise quality assurance. The authorities are under political pressure to liberalize the drugs market as fast as possible, and this involves the registration of many new, imported products. Several registration applications have been made for new generic versions of existing drugs; these call for an assessment of the drugs' quality and bioequivalence. As a result, the workload of regulatory authorities is increasing greatly. The registration of a product, however, does not mean that it is available or its cost reimbursable. In such cases, potentially useful but expensive drugs must therefore be replaced by locally produced medicines, despite possible disadvantages.

Selecting drugs for appropriate therapy

In many European countries, selective drug lists are used to ensure that patients receive the drugs they really need at a reasonable cost. The selection can be made in four different ways:

- using a "need clause" at the registration or licensing stage (as in Norway), to ensure that all the drugs marketed fulfil a medical or economic need;

- creating a positive list (in, for example, institutional and other formularies) which identifies the selected products;
- creating a negative list of categories of products excluded from use in the health care system; and
- using a differential reimbursement system (as in France and Germany), which groups products into categories and reimburses the costs to the consumer at different rates, according to their therapeutic merit.

For the management of a particular therapeutic problem, it is useful to construct a therapeutic hierarchy, moving from the most widely applicable and cost-effective choice to progressively more specialized drugs (with narrow indications) that will be needed for a relatively low number of patients. It must be recognized, however, that the selected drugs may not be suitable for all patients and that a small proportion of patients will require others. Any system of selected drug lists should therefore provide for meeting the needs of these patients whenever possible. This can be done, for example, by specialist evaluation of such cases.

When assessing the benefit of a drug treatment, it is important to consider the clinical effectiveness of the drug. This is defined as the likelihood and extent of the desired clinical effects on the patient. The term efficacy is best avoided, as this refers to any arbitrarily chosen effect, which may or may not be clinically relevant. Efficiency (the ratio of effectiveness to cost) should be considered so that the best use can be made of the resources available.

Indications lacking a firm scientific basis are a questionable justification for selecting drugs. Examples include diseases found only in particular areas, such as the *crise de foie* in France. Selecting drug combinations requires the justification of each component and of its dosage. Drugs whose clinical effectiveness or safety is unclear are often treated inconsistently; some receive the benefit of the doubt while others are excluded from use.

A series of WHO technical reports on the selection and use of essential drugs has laid the groundwork for drug selection. The most recent list, published in 1990, stipulates about 350 products for use

at all levels of the health care system. Only a small proportion of these products is required in primary care; few individual doctors can adequately handle more than 100 drugs. The major considerations in selection are: clear therapeutic need, product quality, the risk-benefit ratio, cost-effectiveness, and the circumstances. The policy to be followed in the selection process involves decisions on the degree of importance to be given to scientific data, the extent of restriction on the use of a drug, and the extent to which pragmatic solutions are to be accepted (such as therapeutic traditions poorly supported by scientific evidence). Selection will vary between localities and levels of the health care system (such as primary care, district hospitals and regional referral centres) and in disaster relief situations.

In the evaluation of therapeutic need, non-drug interventions must be considered simultaneously with drug treatments. For example, a special diet can be used to treat non-insulin-dependent diabetes and hyperlipidaemia, and surgery and radiotherapy can be used in the treatment of cancer.

Drug selection is a continuous process. The list of selected drugs must be reviewed regularly and updated with the assistance of epidemiological information, including drug utilization data. The selection of drugs is only one step in the therapeutic process. For each condition, the selected drugs need to be placed within a sequence, beginning with diagnosis according to widely accepted criteria. The delivery of the drug may involve special technology, such as injection or infusion or the use of aerosol inhalers or nebulizers, and often requires monitoring by the patient or the health professional.

Drug selection is also important to each prescriber. The professional freedom to prescribe whatever seems appropriate must be balanced with public accountability for efficient prescribing.

Promoting rational prescribing patterns

Prescribing and drug use are often irrational and many prescribers are slow to change obsolete habits. Although pharmaceuticals promotion should be accurate and balanced and claims must be based on an

up-to-date evaluation of all available evidence, promotion addresses commercial rather than medical needs. Prescribers are not sufficiently aware of this; most have not been trained to think actively and critically about the use of drugs. A move towards more rational drug use requires well targeted education and comparative information. The two most important means of delivering information on drugs are formularies and bulletins.

The development of formularies in hospitals or in primary care focuses attention on therapeutic issues and gives general practitioners a personal share in collective work. This is particularly valuable when a clinical pharmacologist or a specially trained pharmacist can lend expert assistance. The purpose of a local formulary is only partly economic; the main reason for developing and using a formulary is to provide better treatment for patients. Some countries have national formularies. These formularies (such as the British National Formulary) are a respected and widely used source of up-to-date and reliable information.

Drug bulletins, which exist in most European countries, are the second major source of independent therapeutic information. Their role in medical practice was discussed at a WHO meeting on drug information in 1991. Bulletins can give comparative information on old and new drugs and on non-drug treatment, and thus prompt warnings on newly detected problems, such as adverse drug reactions.

Drug information centres are a third source of useful information for prescribers. Although these centres have primarily served hospital doctors, many are beginning to respond to the needs of primary care.

In addition to informing professionals, patients and the public need to be educated on the properties of medicines to improve the rationality of drug use. Healthy people rarely need to know much about medicines, but patients must understand and be able to use essential information about their medicines. Much progress has been made by providing printed information for patients, and every medicine prescribed in the European Community will eventually be accompanied by a leaflet giving full information in non-technical language about the drug.

It is rare, however, that everyone can be assumed to know the basic underlying principles of drug use: how drugs enter the body, what happens once they are absorbed, how they work, how they are eliminated and how long this process takes. Patients do not know enough about the relationship between dose and effect, that is the higher the dose, the greater the variety of unwelcome and perhaps dangerous effects. Patients cannot distinguish clearly between curative, preventive, symptomatic and replacement or physiologically supportive treatments. These are simple ideas that could easily be taught in schools.

The recent development of information leaflets and the greater accessibility of drug compendia have distracted attention from the need for verbal information and indeed discussion about medicines between the doctor and the patient and between the pharmacist and the patient. A leaflet or an entry in a book can only be general, because it must apply to all patients taking a particular medicine. The doctor and pharmacist should therefore emphasize to the patient the information that is relevant and specific to that person. Communication between the patient and the professional will work optimally when both parties actively contribute. It would be useful to prompt the patient with a list of relevant and important questions about the medicine he or she is taking; he or she should know the answers. Doctors and pharmacists should take the initiative by encouraging patients to ask these questions; a leaflet listing specific questions could be distributed to pharmacies and available in doctors' waiting rooms.

Adverse reactions pose a special problem, not least because drug injury is a major public health problem. While giving patients a complete account of possible adverse reactions is undesirable and impractical, patients must be informed about common or important reactions that require some action. Information for patients can be produced in many languages and leaflets for minority groups will be valuable in many countries. The practical problems of providing this information to health professionals caring for such groups should be overcome as soon as possible.

The education of medical students in clinical pharmacology and therapeutics has not hitherto resulted in better prescribing skills.

These skills encompass the rational use of facts about drugs and not just the possession of the facts. Teaching modules on prescribing skills are being developed at the WHO Collaborating Centre for Clinical Pharmacology and Drug Policy Science[a] and will be tested in eight medical schools around the world.

Ensuring the quality of clinical trials

The results of clinical trials are the basis upon which drugs are approved and licensed, and should support their therapeutic use. The need to ensure that such results are accurate and reliable led to a more systematic critical assessment and rigorous control by both the scientific community and regulatory authorities in general. This assessment and control should ensure that results are good enough to be included in systematic overviews (meta-analyses) of groups of trials addressing a particular question.

Regulatory authorities should be encouraged to exchange evaluation reports on applications for product licences. This will enable an authority to use the critical assessments of important trials made by experts in other countries.

The problem of fraud has led to the development of guidelines for good clinical practice, which relate to the conduct and documentation of clinical trials. The use of these guidelines requires precise and accurate data and an ability to inspect trials on site. The introduction of the guidelines by regulatory authorities will help to ensure that trials are correctly performed, although compliance requires a change in attitude and extra work by clinical investigators and their sponsors.

The role of governments is to provide the legal framework for clinical trials. Such a framework should allow only trials of good quality, and protect the safety and rights of the subjects taking part. Appropriate ethics committees should approve protocols for clinical trials; their work should be governed by national regulations incorporating the content of relevant international conventions, such as the Declaration of Helsinki.

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[a] Information can be obtained from Mr T. de Vries, Department of Pharmacology/Clinical Pharmacology, University of Groningen, Bloemsingel 1, 9713 BZ Groningen, Netherlands.

The critical evaluation of trial protocols is a skilled task to be performed during the planning of a trial, to allow for any corrections. Regulatory officials with wide experience can often assist companies and investigators to improve trial design. Creating capacities to perform clinical trials of high standard is a task needing resources and time. Clinical investigators, sponsors or monitors, and regulatory officials all need education in clinical trial methodology, to which academic institutions, industry and government agencies should contribute.

Trials in general practice pose special problems. Although these are needed mainly for treatments in primary care, few general practitioners are adequately trained as investigators and in the coordination of multicentre clinical trials. Such trials have been conducted inadequately, although steps to improve their quality are being taken. Building an adequately clinical trial capability in general practice in countries that lack it may take years.

Drug promotion

Drug promotion and marketing powerfully influence the prescribing behaviour of professionals and self-medication by the public. At present the promotion of individual prescription medicines is controlled to some extent by legislation and partial self-regulation by the pharmaceuticals industry (under the code of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) and the various codes of the pharmaceuticals industry in countries). Neither form of regulation, however, is sufficient to harmonize the promotion of medicines with rational drug therapy. There is an inherent conflict of interest between the legitimate business goals of manufacturers and the social, medical and economic needs of providers and the public to select and use drugs in the most rational way.

The promotion of nonprescription or over-the-counter medicines is intended to inform the consumer that a product exists and what it can offer. Although warnings and contraindications should be included in advertisements of nonprescription drugs, this information is best communicated on the label or on accompanying leaflet

and by the pharmacist. For this reason, a brief general statement such as "use only as directed" or "always read the label" may be sufficient for the advertisement.

Conclusions and recommendations

1. The criteria for drug selection developed by WHO should be adopted, in accordance with policies established at the national level.

2. The principles upon which drugs are selected after registration should be: their effectiveness and safety for particular indications and their quality, convenience and cost. Since a drug may be selected for only one of several indications, it is desirable to state the indications for all drugs selected.

3. The selection of drugs for rational and cost-effective use requires the active participation of clinicians, clinical pharmacologists, pharmacists and health economists. Each country needs to identify national and international resource people within these categories. Scientifically valid data are essential for the drug selection process and should be obtained from the pharmaceuticals industry, as well as other sources.

4. Hierarchies of treatment should be recommended in the management of particular problems, beginning with the most widely applicable and cost-effective treatment and ending with those with the most specialized and narrow indications.

Since drugs are only one element of a therapeutic strategy, the selection process must include non-drug elements such as diagnostic procedures, surgery and follow-up systems. This is especially important in dealing with chronic diseases (such as diabetes, peptic ulcers, asthma and epilepsy). Therapeutic strategies should be considered on an international basis when possible.

5. Doctors and pharmacists should be encouraged to play an active part in systematic drug selection in their communities. They should also receive training in the economics of the rational use of drugs.

6. Training in all aspects of drug control, including the scrutiny and critical evaluation of data, should be organized for regulators and politicians concerned with drug policies, particularly those in countries of the central and eastern parts of the European Region. Communication between regulators in different European countries should be facilitated by means of meetings and similar activities.

7. Programmes should be developed to train health economists in the economic aspects of rational drug use, so that their expertise can be used by the health professions.

8. Mutual assistance between regulatory authorities in central and eastern European countries should be systematically developed, possibly along the lines of the earlier cooperation in CMEA. Critical scientific evaluation reports, which assist regulatory authorities to assess new products, should be made available to authorities in Europe and beyond. Informal contacts between regulatory authorities should also be encouraged.

9. WHO should assist governments desiring to establish efficient national drug regulatory agencies and to build the computer capability for drug registration to be carried out by these agencies.

10. Training in clinical pharmacology is essential in undergraduate and postgraduate medical education and should continue throughout a doctor's professional life. The inclusion of training in prescribing skills in the medical curriculum should be emphasized. These skills would include the rational use of facts about drugs instead of the simple possession of the facts. Students should learn how to choose and prescribe drugs, and to formulate a policy for follow-up, instead of being told what to choose.

11. Medical and pharmacy students, as well as doctors and pharmacists, need training in informing their patients about treatment. Such training should be given in both primary care and hospitals.

12. Health professionals should be provided with regular, objective, up-to-date information about medicines, particularly comparative information, in a form that is easy to use in practice, such as a national formulary or a drug bulletin.

13. WHO should contribute to educating and informing professionals through such means as organizing workshops for the exchange of experience and therapeutic strategies.

14. Steps should be taken to inform prescribers about the cost of treatments.

15. Therapeutic self-audit and peer audit should become a regular part of a doctor's work.

16. Patients need verbal and written information about their treatment. Information leaflets, summarizing the essential points in easily understood language, should be made available to patients in addition to personal explanations provided by doctors, nurses and pharmacists. A list of simple questions that patients can ask their doctors and/or pharmacists about their medicines should be widely distributed, for example, in pharmacies and doctors' waiting rooms.

17. The basic ideas that underlie the use of drugs should be taught in schools.

18. National drug laws should specify standards to ensure high scientific quality in the performance and supervision of clinical trials.

19. WHO should continue to promote the international harmonization of the requirements for clinical trials that are intended to document the efficacy and safety of pharmaceutical products.

20. WHO should facilitate implementation of guidelines on good clinical practice in clinical trials implemented in its Member States.

21. Steps should be taken to harmonize the structure, practice and authority to act of research ethics committees in countries.

22. Governments should introduce or amend regulations to take account of ethical criteria developed by WHO and the pharmaceuticals industry for the promotion of drugs, and monitor compliance with these regulations.

23. Governments should require that the international nonproprietary or approved generic names of drugs appear on the packages and labels of and the promotional material for prescription medicines; this information should appear in print of the same size and type-face as that used for the brand name.

24. Governments should require that the international nonproprietary name, the established name or approved generic name be placed prominently on the main display panel of packaged nonprescription medicines and in promotional material. This should also apply to combination products unless the number of active ingredients makes it impractical.

Annex 1

WORKING PAPERS[a]

ICP/DSE 173/6	The status of drug research, production and control in countries in central and eastern Europe, by G. Guencheva
ICP/DSE 173/7	Drug supply and prescribing patterns in central and eastern Europe, by J. Svihovec
ICP/DSE 173/8	Selective drug lists in Europe: scope and limitations, by K. Quiring
ICP/DSE 173/9	Overview of selective drug lists in Europe, by J. Borvendeg
ICP/DSE 173/10	Selection criteria for drug lists, by P.K.M. Lunde
ICP/DSE 173/11	Improving the prescribing and drug use by information to doctors and other health care personnel, by E. Gysling

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